May an adrenal incidentaloma change its nature?

May an adrenal incidentaloma change its nature?

Alessandra Müller[1], Elisa Ingargiola[1], Federica Solitro[2], Enrico Bollito[3], Soraya Puglisi[1*], Massimo Terzolo[1], Anna Pia[1], Giuseppe Reimondo[1**].**

** have equally contributed as senior authors

[1] Internal Medicine, Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital, University of Turin, Orbassano, Italy

[2] Radiology, Department of Oncology, San Luigi Gonzaga Hospital, University of Turin, Orbassano, Italy

[3] Pathology, Department of Oncology, San Luigi Gonzaga Hospital, University of Turin, Orbassano, Italy

* Corresponding Author: **Soraya Puglisi**

Internal Medicine, Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital, Regione Gonzole 10, 10043 Orbassano, Italy; tel: +39 011 9026292, fax: +39 011 6705456

e-mail: sorayapuglisi@yahoo.it ORCID: 0000-0002-2883-6139

Keywords: incidentaloma, adrenal tumor, metastasis, PET, uptake, adrenalectomy, follow-up, lung cancer.

Author Contributions: Clinical management of the patient: AP; Imaging review: FS; Pathological review: EB; Drafting of the Manuscript: AM, EI; Critical Review of the Manuscript: SP, AP, GR, MT; Supervision: AP, GR, MT.

Abstract

Up to 70% of adrenal masses detected in patients affected by extra-adrenal malignancy are metastatic lesions. Therefore, detection of an adrenal mass in patients with active or previous malignancy requires a careful differential diagnostic work-up. ^{18}F-Fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) is increasingly used to determine the malignant potential of adrenal lesions.

We report the case of a 64-year-old man who had a single adrenal metastasis due to non-small-cell lung carcinoma developing on a pre-existing benign adrenal lesion. This metastasis occurred in a phase of perceived oncological remission and was detected thanks to ^{18}F-FDG-PET/CT showing a focal adrenal uptake. Contrast-enhanced computed tomography (CT), performed as part of oncological follow-up, and MRI with chemical shift sequences did not lead to the correct diagnosis. The patient underwent laparoscopic adrenalectomy and the pathological evaluation confirmed a lung carcinoma metastasis.

The present case highlights the peculiarity of the follow-up of adrenal masses in cancer patients and the primary role of ^{18}F-FDG-PET/CT in the management of such patients.

Background

About 2% of all incidentally detected adrenal masses are of metastatic nature. This percentage rises to 30-70% in patients affected by an extra-adrenal malignancy [1] . The adrenal gland represents indeed a frequent site of metastasis, due to its rich sinusoidal vascularization. Lung cancer followed by breast cancer and melanoma are most likely to spread to the adrenal gland [2] . Rare cases of collision tumors, defined as the coexistence of two different tumors in an adrenal gland, such as an adrenal adenoma and an adrenal cancer or a metastatic tumor, have been described [3].

Although no randomized study comparing imaging tests has been performed, non-contrast computed tomography (CT) is generally considered as the first-line imaging test to make a differential diagnosis between benign and malignant adrenal masses. Whenever the mass is considered of indeterminate nature after non-contrast CT, second-line imaging tests, including CT with delayed contrast media washout, chemical shift MRI, and ^{18}F-FDG-PET/CT, are needed to define the diagnosis [4]. Once that an adrenal incidentaloma is considered to be a benign lesion after an appropriate work-up, it is not recommended to pursue a specific follow-up with repeated imaging studies [4]. The recommendation is based on the very low chance that a benign adrenal lesion may turn in a malignant one during follow-up [5].

We report here in a case that represents an exception to this general rule and underlines the challenges that may arise in the diagnosis of adrenal metastases.

Case presentation

The patient is a 64-year-old man, ex-smoker (10 cigarettes/day), with an occupational exposure to silica dust and asbestos and a clinical history of chronic obstructive pulmonary disease and arterial hypertension. In 2008, a left adrenal nodule was occasionally detected and investigated with

endocrinological workup and non-contrast CT, which were suggestive for a benign, non-functioning, adrenal adenoma. The lesion was of 30 mm in size with a density < 0 Hounsfield Units (HU) [Figure 1].

In August 2015, a squamous cell carcinoma of the upper lobe of the right lung with mediastinal lymphadenopathy was diagnosed. The patient was treated with chemo- and radiotherapy with complete disease response and subsequent negative radiological follow-up.

In September 2017, a follow-up total body contrast-enhanced CT scan showed multiple pulmonary lesions and a slight enlargement of the known left adrenal nodule (37 mm diameter) [Figures 2a and 2b]. Hounsfield Units and morphological characteristics were not reported. Due to the suspect of disease recurrence a ^{18}F-FDG-PET/CT scan was performed and it showed a focal pathological uptake in the left adrenal region without relevant uptakes in other sites (absolute SUV value 7.8, adrenal/liver ratio 3.5) [Figure 2c], while the pulmonary lesions resolved after antibiotic therapy.

The patient was then referred to our outpatient unit. A hormonal workup was negative for hypercortisolism, primary hyperaldosteronism and catecholamine excess. All the available CT scans were re-evaluated by an expert radiologist, who confirmed the increase in size (7 mm) and described the adrenal mass as inhomogeneous with faintly irregular borders. Due to the changed radiological characteristics an adrenal magnetic resonance imaging (MRI) with chemical shift sequences was performed but was not conclusive in the differential diagnosis between a lipid-poor adenoma and a malignant lesion, showing incomplete, inhomogeneous signal intensity loss in out-of-phase sequences [Figures 3a and 3b].

Following the pathological adrenal uptake at FDG-PET scan, not justified by an autonomous hormone production, and the undetermined radiological characteristics at MRI the patient underwent left laparoscopic adrenalectomy with an uneventful course. The pathological exam revealed that the adrenal parenchyma was completely replaced by squamous carcinoma cells, with typical adenomatous cells surrounding the central neoplastic core [Figures 4a and 4b].

4

Discussion

Whether most adrenal masses detected in patients affected by extra-adrenal malignancies are of secondary nature, adrenal metastases are rarely found in non-oncological patients [1]. Therefore, a history of known extra-adrenal malignancy requires a particular attention to the possibility of an adrenal metastasis. A new adrenal lesion developing during oncological follow-up should also be viewed as suspicious.

In clinical practice, the most commonly used imaging techniques to assess the risk of malignancy are: non-contrast CT, MRI with chemical shift sequences, and ^{18}F-FDG-PET/CT. The recent ESE/ENSAT guidelines on the management of adrenal incidentalomas recommended non-contrast CT as the first radiological test [4]. Adrenal lesions that are homogeneous, smaller than 4 cm, with density < 10 Hounsfield units (HU) are considered benign, lipid-rich adenomas. However, about 30% of adrenal adenomas are lipid-poor and show an attenuation value > 10 HU that overlaps with malignant lesions and pheochromocytomas [6-8]. The use of MRI with chemical shift sequences is based on the typical loss of signal intensity shown by intracellular lipid-rich lesions in out-of-phase sequences, while lipid-poor adenomas, malignant lesions and pheochromocytomas remain unchanged [9-11]. In patients with history of extra-adrenal malignancy, the ESE/ENSAT guidelines suggest the use of ^{18}F-FDG-PET/CT performed as part of oncological follow-up [4]. ^{18}F-FDG-PET/CT has the advantage of being able to detect malignant adrenal lesions with a low rate of false negatives (mainly metastases from tumors with low FDG-uptake, i.e. kidney cancer [12]) and a certain rate of false positives (i.e., functional adenomas [13]) [14]. Routine use of ^{18}F-FDG-PET/CT in patients without history or suspect of malignancy is currently not recommended, but a recent prospective study showed that it has an excellent negative predictive value in the characterization of indeterminate and/or large adrenal masses in non-cancer patients [15].

In our patient, the contrast-enhanced CT performed during the oncological follow-up reported only a slight enlargement of the known adrenal lesion and only the radiological revision, requested after the ^{18}F-FDG-PET/CT, showed changes of the lesion's features. The ^{18}F-FDG-PET/CT was done primarily for the suspect of pulmonary progression of disease but showed a single, focal uptake of the known adrenal lesion. Since the mass has been previously recognized as benign, further diagnostic tests were done. Hormone assessment was unrewarding, and MRI was still compatible with a lipid-poor adenoma. Our case represents a "real-life" demonstration of the limits of radiological and functional imaging in defining adrenal masses nature, especially in patients with known oncological history. These limits have been widely analyzed in a systematic review and meta-analysis [16] which laid the groundwork for the recommendations given by the ESE/ENSAT guidelines, especially when second-line imaging techniques are used in indeterminate adrenal masses. Despite the great potential of available radiological and functional imaging, there are not only difficulties related to the heterogeneity of both benign and malignant adrenal lesions and to the frequent overlap in imaging features [17], but also the expertise of the single radiologist and clinician influence the patient's diagnostic pathway in clinical practice.

In our patient, since radiological and functional imaging were not conclusive in defining the nature of the adrenal lesion's changes, a histopathological evaluation was considered essential. The multidisciplinary team discussion considered the adrenal biopsy a possible choice, but since we had a consistent suspicion of malignancy and the patient was in excellent clinical conditions with a prolonged disease-free interval following oncological treatment of his non-small cell lung cancer (NSCLC), we decided to be proactive and recommended surgical removal of the adrenal lesion. Our choice was also supported by the expertise of our surgeon and the notion of a favorable outcome of patients who underwent removal of solitary adrenal metastases from different cancer types, including NSCLC.

6

Since the first description of adrenalectomy for isolated metastasis in 1982 [18], many retrospective series showed a potential benefit in survival in well-selected patients undergoing surgical treatment [19-26].

In recent years, there is growing evidence in support of use of laparoscopic approach in malignant adrenal lesions ensuring an adequate oncologic result, in addition to the advantages of mini-invasive surgery in terms of safety and post-operative recovery [27-30]. Therefore, laparoscopic adrenalectomy represents the first-choice surgical option in these patients.

Given the low probability that a benign adrenal lesion becomes malignant during follow-up [5], an active imaging surveillance of adrenal incidentalomas that are characterized to be benign is currently not recommended [4, 31]. However, oncological patients may represent a possible exception to the rule because neoplastic cells may be seeded in a pre-existing benign lesion. Whether the coexistence of a metastasis in an adrenal benign lesion is an incidental occurrence or represents the result of changes in the local environment that may favor hematogenous metastatization in an adrenal adenoma is not still clear. In 2014, Untch and colleagues [3] reviewed 11 histopathologically-proved adrenal collision tumors described in literature. In the last five years other 14 case reports of adrenal collision tumors have been published [3, 32-51]. The 25 cases are summarized in Table 1. In 18 cases, an adrenal adenoma was present. In 17 cases a malignant component was described, in 6 cases of primitive adrenal origin, in 11 cases of metastatic nature. 3 cases were lung cancer metastases, one small cell lung carcinoma (SCLC) and two NSCLC.

Conclusions

In conclusion, we have reported the development of a solitary adrenal metastasis on a pre-existing benign adrenal lesion in a patient with a NSCLC in apparent clinical remission. Although oncologists

and pneumologists, familiar with the way of metastatic spreading of lung carcinoma, are used to follow up patients with total body CT, this case report highlights the peculiarity of the follow-up of adrenal masses in cancer patients. While imaging follow-up of adrenal incidentalomas is seldom recommended [4, 5, 31] any adrenal lesion in a patient with known oncological disease should be carefully evaluated at any restaging, even if the mass has been previously labelled as benign. This is of utmost importance when a complete response of the primary cancer has been obtained after treatment, since the detection of new adrenal metastasis may change the management plan. In this clinical scenario, ^{18}F-FDG-PET/CT represents a valid tool to guide clinicians in the decision-making process [52].

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

REFERENCES

1. Terzolo M, Stigliano A, Chiodini I, Loli P, Furlani L, Arnaldi G et al. (2011) AME position statement on adrenal incidentaloma Eur J Endocrinol 164:851-70.
2. Cingam SR, Karanchi H (2019) Cancer, Adrenal Metastasis. StatPearls Publishing
3. Untch BR, Shia J, Downey RJ, Carrasquillo JA, Panicek DM, Strong VE (2014) Imaging and management of a small cell lung cancer metastasis/adrenal adenoma collision tumor: a case report and review of the literature. World J Surg Oncol 12:45.
4. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A et al. (2016) Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors Eur J Endocrinol 175:G1-G34.
5. Elhassan YS, Alahdab F, Prete A, Delivanis DA, Khanna A, Prokop L et al. (2019) Natural History of Adrenal Incidentalomas With and Without Mild Autonomous Cortisol Excess: A Systematic Review and Meta-analysis Ann Intern Med 171:107-116.

8

6. Caoili EM, Korobkin M, Francis IR, Cohan RH, Dunnick NR (2000) Delayed enhanced CT of lipid-poor adrenal adenomas AJR Am J Roentgenol 175:1411-5.

7. Peña CS, Boland GW, Hahn PF, Lee MJ, Mueller PR (2000) Characterization of indeterminate (lipid-poor) adrenal masses: use of washout characteristics at contrast-enhanced CT Radiology 217:798-802.

8. Zhang HM, Perrier ND, Grubbs EG, Sircar K, Ye ZX, Lee JE, et al. (2012) CT features and quantification of the characteristics of adrenocortical carcinomas on unenhanced and contrast-enhanced studies Clin Radiol 67:38-46.

9. Dunnick NR, Korobkin M (2002) Imaging of adrenal incidentalomas: current status AJR Am J Roentgenol 179:559-68.

10. Haider MA, Ghai S, Jhaveri K, Lockwood G (2004) Chemical shift MR imaging of hyperattenuating (>10 HU) adrenal masses: does it still have a role? Radiology 231:711-6.

11. Bharwani N, Rockall AG, Sahdev A, Gueorguiev M, Drake W, Grossman AB, et al. (2011) Adrenocortical carcinoma: the range of appearances on CT and MRI AJR Am J Roentgenol 196:W706-14.

12. Zukotynski K, Lewis A, O'Regan K, Jacene H, Sakellis C, Krajewski K, et al. (2012) PET/CT and renal pathology: a blind spot for radiologists? Part 1, primary pathology AJR Am J Roentgenol 199:W163-7.

13. Alencar GA, Fragoso MC, Yamaga LY, Lerario AM, Mendonca BB (2011) (18)F-FDG-PET/CT imaging of ACTH-independent macronodular adrenocortical hyperplasia (AIMAH) demonstrating increased (18)F-FDG uptake J Clin Endocrinol Metab 96:3300-1.

14. Ansquer C, Scigliano S, Mirallié E, Taïeb D, Brunaud L, Sebag F, et al. (2010) 18F-FDG PET/CT in the characterization and surgical decision concerning adrenal masses: a prospective multicentre evaluation Eur J Nucl Med Mol Imaging 37:1669-78.

15. Guerin C, Pattou F, Brunaud L, Lifante JC, Mirallié E, Haissaguerre M, et al. (2017) Performance of 18F-FDG PET/CT in the Characterization of Adrenal Masses in Noncancer Patients: A Prospective Study J Clin Endocrinol Metal 102:2465-72.

16. Dinnes J, Bancos I, Ferrante di Ruffano L, Chortis V, Davenport C, Bayliss S, et al (2016) Imaging for the diagnosis of malignancy in incidentally discovered adrenal masses – a systematic review and meta-analysis Eur J Endocrinol 175: R51-64.

17. Albano D, Agnello F, Midiri F, Pecoraro G, Bruno A, Alongi P et al. (2019) Imaging features of adrenal masses. Insights Imaging 10:1.

18. Twomey P, Montgomery C, Clark O (1982) Successful treatment of adrenal metastases from large-cell carcinoma of the lung JAMA 248:581-3.

19. Vazquez BJ, Richards ML, Lohse CM, Thompson GB, Farley DR, Grant CS, et al. (2012) Adrenalectomy improves outcomes of selected patients with metastatic carcinoma World J Surg 36:1400-5.

20. Higashiyama M, Doi O, Kodama K, Yokouchi H, Imaoka S, Koyama H (1994) Surgical treatment of adrenal metastasis following pulmonary resection for lung cancer: comparison of adrenalectomy with palliative therapy Int Surg 79:124-9.

21. Kim SH, Brennan MF, Russo P, Burt ME, Coit DG (1998) The role of surgery in the treatment of clinically isolated adrenal metastasis Cancer 82:389-94.

22. Porte H, Siat J, Guibert B, Lepimpec-Barthes F, Jancovici R, Bernard A, et al. (2001) Resection of adrenal metastases from non-small cell lung cancer: a multicenter study Ann Thorac Surg 71:981-5.

23. Pfannschmidt J, Schlolaut B, Muley T, Hoffmann H, Dienemann H (2005) Adrenalectomy for solitary adrenal metastases from non-small cell lung cancer Lung Cancer 49:203-7.

24. Tanvetyanon T, Robinson LA, Schell MJ, Strong VE, Kapoor R, Coit DG, et al. (2008) Outcomes of adrenalectomy for isolated synchronous versus metachronous adrenal metastases in non-small-cell lung cancer: a systematic review and pooled analysis J Clin Oncol 26:1142-7.

25. Raz DJ, Lanuti M, Gaissert HC, Wright CD, Mathisen DJ, Wain JC (2011) Outcomes of patients with isolated adrenal metastasis from non-small cell lung carcinoma Ann Thorac Surg 92:1788-93.

26. Ramsingh J, O'Dwyer P, Watson C (2019) Survival outcomes following adrenalectomy for isolated metastases to the adrenal gland Eur J Surg Oncol 45:631-4.

27. Marangos IP, Kazaryan AM, Rosseland AR, Røsok BI, Carlsen HS, Kromann-Andersen B, et al (2009) Should we use laparoscopic adrenalectomy for metastases? Scandinavian multicenter study J Surg Oncol 100:43-7.

28. Moreno P, de la Quintana Basarrate A, Musholt TJ, Paunovic I, Puccini M, Vidal O, et al. (2013) Adrenalectomy for solid tumor metastases: results of a multicenter European study Surgery 154:1215-23.

29. Puccini M, Panicucci E, Candalise V, Ceccarelli C, Neri CM, Buccianti P, et al. (2017) The role of laparoscopic resection of metastases to adrenal glands Gland Surg 6:350-4.

30. Drake FT, Beninato T, Xiong MX, Shah NV, Kluijfhout WP, Feeney T, et al. (2019) Laparoscopic adrenalectomy for metastatic disease: Retrospective cohort with long-term, comprehensive follow-up Surgery 165:958-64.

31. Terzolo M, Reimondo G (2019) Insights on the Natural History of Adrenal Incidentalomas Ann Intern Med 171:135-136.

32. Pakalniskis MG, Ishigami K, Pakalniskis BL, Fujita N (2019). Adrenal collision tumour comprised of adrenocortical carcinoma and myelolipoma in a patient with congenital adrenal hyperplasia. J Med Imaging Radiat Oncol.

33. Foresti M, Parmiggiani A (2019) Adrenal Adenoma-Hemangioma Collision Tumor: Description of Two Cases. J Radiol Case Rep 13:1-12.

34. Khorsand A, Khatami F, Sefidbakht S, Saffar H, Sadeghipour A, Tavangar SM (2018) Adrenal Collision Tumor Composed of Pheochromocytoma and Diffuse Large B-Cell Lymphoma: A Case Report. Int J Hematol Oncol Stem Cell Res 12:249-252.

10

35. Lai Y, Zhou L, Hu J, Li W, Cui L, Lai Y, Ni L (2018) Erratum: Adrenal collision tumor (parachordoma and ganglioneuroma): A case report. Mol Clin Oncol 9:238.
36. Zhang CX, Tian Y (2018) Adrenal Collision Tumor Composed of Adrenocortical Adenoma and Pheochromocytoma. Chin Med J (Engl). 131:374-375.
37. Liu D, Kumar SA (2017) An exceedingly rare adrenal collision tumor: adrenal adenoma-metastatic breast cancer-myelolipoma. J Community Hosp Intern Med Perspect 7:241-244.
38. Takizawa K, Kohashi K, Negishi T, Taguchi K, Yamada Y, Nakamura M, et al (2017) A exceptional collision tumor of primary adrenal angiosarcoma and non-functioning adrenocortical adenoma. Pathol Res Pract 213:702-705.
39. Lee HS, Choi YJ, Kim C, Kim BH (2016) Adrenal Collision Tumor: Coexistence of Pigmented Adrenal Cortical Oncocytoma and Ganglioneuroma. Case Rep Surg 5790645.
40. Piotrowski Z, Tomaszewski JJ, Hartman AL, Edwards K, Uzzo RG (2015) Renal cell carcinoma and an incidental adrenal lesion: adrenal collision tumors. Urology 85:e17-8.
41. Hayashi T, Gucer H, Mete O (2014) A mimic of sarcomatoid adrenal cortical carcinoma: epithelioid angiosarcoma occurring in adrenal cortical adenoma. Endocr Pathol 25:404-9.
42. Wang J1, Fisher C1, Thway K2 (2014) "Dominant" myelolipoma encasing adrenal cortical carcinoma: an unusual variation of myelolipoma occurring as a synchronous and predominant neoplasm Int J Surg Pathol 22:731-5.
43. Abdullazade I. S., Tezel G (2012) A rare case of collision tumor: coexistence of adrenocortical adenoma and pheochromocytoma in the same adrenal gland Journal of Medical Cases 3:63–67.
44. Siddiqi AJ, Miller FH, Kasuganti D, Nikolaidis P (2009) Adrenal hemangioma-adenoma: an exceedingly rare adrenal collision tumor. J Magn Reson Imaging 29:949-52.
45. Bertolini F, Rossi G, Fiochhi F, Giacometti M, Fontana A, Gibertini MC, et al. (2011) Primary adrenal gland carcinosarcoma associated with metastatic rectal cancer: a hitherto unreported collision tumor Tumori 97:27e–30e.
46. Thorin-Savoure A, Tissier-Rible F, Guignat L, Pellerin A, Bertagna X, Bertherat J, et al. (2005) Collision/composite tumors of the adrenal gland: A pitfall of scintigraphy imaging and hormone assays in the detection of adrenal metastasis J Clin Endo Metabol 90:4924–4929.
47. Hagspeil KD (2005) Manifestation of Hodgkin's lymphoma in an adrenal myelolipoma Eur Radiol 15:1757–1759.
48. Blake MA, Sweeney AT, Kalra MK, Maher MM (2004) Collision adrenal tumors on PET/CT AJR Am J Roentgenol 183:864–865.
49. Otal P, Escourrou G, Mazerolles C, Janne d'Othee B, Mezghani S, Musso S, et al. (1999) Imaging features of uncommon adrenal masses with histopathologic correlation Radiographics 19:569–581.
50. Schwartz LH, Macari M, Huvos AG, Panicek DM (1996) Collision tumors of the adrenal gland: demonstration and characterization at MR Imaging. Radiology 201:757–760.
51. Hoshi H, Jinnouchi S, Ono S, Kihara Y, Arakawa K, Takeuchi M, et al. (1984) Scintigraphic demonstration of coexisting adenoma and metastasis of the adrenal gland in a patient with bronchogenic carcinoma. Clin Nucl Med 9:717–718.

52. Kandathil A, Wong KK, Wale DJ, Zatelli MC, Maffione AM, Gross MD, et al. (2015) Metabolic and anatomic characteristics of benign and malignant adrenal masses on positron emission tomography/computed tomography: a review of literature Endocrine 49:6-26.

12